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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,119	BACUS, SARAH S.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1,2 and 4-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1,2 and 4-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/17/04; ~~5/5/05~~. 4/5/05 KAC 7/09/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim 1 has been amended. Claims 1, 2 and 4-6 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 1, 2 and 4-6 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 1 is drawn to a method for determining a response to administration of a cancer chemotherapeutic or chemopreventative agent comprising collecting a first tissue or cell sample from an individual before exposing the individual to the cancer chemotherapeutic or chemopreventative agent; collecting a second tissue or cell sample from the individual after exposing the individual to the cancer chemotherapeutic or chemopreventative agent; staining the first and the second tissue or cell samples with one of a multiplicity of stains that are either X-Gal, or both X-Gal and a detectably labeled antibody directed against a biological marker, wherein the biological marker is p21, p27, p16, TGF-beta or SA-Beta-Gal; measuring the optical density of the stained cells of step (c) wherein the stained cells are illuminated with light having a wavelength absorbed by the stain; determining whether expression of the biological marker associated with apoptosis was increased following exposure to the chemotherapeutic or chemopreventative agent. Claim 2 embodies the method of claim 1 wherein the detectable label is a chromogen or fluoraphore. Claim 4 embodies the method of claim 1 wherein the amount of

biological marker protein is determined by ELISA assay. Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is preformed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is preformed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells.

(A) As drawn to "tissue or cell samples" and the lack of correlation between TGF-beta, p21, p16 and p27 with the states of apoptosis, terminal differentiation and senescence within said "tissue or cell samples" treated by a cancer chemotherapeutic agent.

The instant claims are draw to a method of determining a response to administration of a cancer chemotherapeutic or chemopreventative agents to an individual comprising determining whether expression of a biological marker was increased in a tissue or cellular sample taken from the individual following exposure to said chemotherapeutic or chemopreventative agent, wherein said biological marker includes p21, p27, p16, TGF-beta and SA-B-gal.

The art teaches that the relationship between the expression of p16, p21, p27 and TGF-beta resulting from cancer chemotherapy is complex. For instance, Morris et al (Biochemical and Molecular Medicine, 1997, Vol. 60, pp. 108-115), teach that treatment of Raji lymphoma in vivo with methylprenisolone causes a reduction in the level of tumor growth, however, no change in the level of TGF-beta was observed and CDKN1 (p21) was decreased rather than increased as required by the instant method. The abstract of Sethi et al (Proc Annu Meet Am Soc Clin Oncol, 1996, Vol. 15, pp. A1308) teaches that the expression of Bcl2 in lymphomas confounds the apoptosis inducing effect of TGF-beta thus detection of an increase in TGF-beta by a lymphoma cell that concurrently over expressed Bcl2 would not be expected to be indicative of apoptosis. Urashima et al (Blood, 1997, Vol. 90, pp. 4106-4115) teach that the p16 gene is frequently deleted in lymphoblastic leukemia associated with the growth of less differentiated tumor cells. Although the abstract teaches that ectopic expression of p16 in the p16-negative cells suppresses cell growth, the specification provides no teaching regarding how the level of p16 is to be increased as a result of chemotherapy in a sample of leukemia cells having a deleted p16 gene. The specification fails to provide objective evidence that cells undergoing apoptosis as a result of cancer chemotherapy would exhibit an increased expression

of p16 relative to the same cell in the non-apoptotic state. Further Wang et al (International Journal of Oncology, 1999, Vol. 15, pp. 1097-1102) teach that cisplatin, a cancer chemotherapy agent, induced a senescence-type growth arrest in human tumor cell lines without an alteration in the level of either p16 or p21. Thus, one of skill in the art would not be able to interpret the significance attached to the level of p21 or p16 exhibited by a human tumor cell after exposure to the chemotherapeutic agent of cisplatin.

In order to use the expression of p21, p16, TGF-beta or p27 as a marker of a positive therapeutic effect resulting from exposure to a chemotherapeutic agent, it would be necessary to assay for said marker within a specific time period after the administration of said chemotherapeutic agent to a patient in need thereof. Li et al (Leukemia and Lymphoma, 1994, Vol. 13, suppl. 1, pp. 65-70) teach that apoptosis of leukemic cells was seen between 8 to 24 hrs after the administration of DNA topoisomerase inhibitors but 48-72 hours after the administration of Taxol or Ara-C. However, the instant claims encompass the analysis of cells taken from individuals which are not limited to cancer cells or to leukemic cells, and the administration of chemotherapeutic agents which are not limited to topoisomerase inhibitors, taxol or Ara-C or other anti-leukemic agents. It is the nature of apoptotic cells that they disintegrate into small pieces and are eliminated by the phagocytic cells of the immune system. It would be necessary to first determine the time frame of apoptosis induction by means of observing DAN strand breaks before proceeding to determine if TGF-beta, p21, p16 or p27 was thereby increased for any sample of tissue or cells taken from an individual who had received any chemotherapeutic agent. This would be further complicated by the fact that if the dosage of the chemotherapeutic agent wax insufficient or the cells were resistant to said chemotherapeutic agent, apoptosis would not be in evidence (the abstract of Cen et al, Zhonghua nei ke za zhi [Chinese Journal of Internal Medicine] 1997, Vol. 36, pp. 300-303. Thus, one of skill in the art would be forced into first determining if, and at what dose, the chemotherapeutic agents causes apoptosis in the patient by assaying for morphological characteristics consistent with apoptosis before it could be determined if any of TGF-beta, p21, p16 or p27 were increased as a result of the chemotherapeutic agent in order to determine the significance of the labeling of the tissue sample with antibodies for TGF-beta, p21, p16 and p27 after exposure to a chemotherapeutic agent. It is noted that for a marker associated only with senescence or terminal differentiation,

the timing of the assay would not be as critical because the terminally differentiated or senescent cell would not be destined for disintegration or attack by a phagocytic cell.

Cohen et al (Biochemical Society Symposium, 1998, Vol. 63, pp. 199-210) teach that activation of Her-3 results in an increase in p21 nuclear staining. However, the abstract of Bacus et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, A3945) teaches that the induction of p21 in breast cancer cell lines in response to doxorubicin fails to occur in cell expressing mutated or dominant negative p53. This is corroborated by Chang et al (Oncogene, 1999, Vol. Vol. 18, pp. 4808-4818, reference of the IDS filed November 19, 2002) who teach that doxorubicin treatment of a tumor cell line resulted in induction of increased levels of p21 which was completely confounded by the same cells transfected with a dominant negative p53 gene (page 4811, lines 19-29). Thus, one of skill in the art would be forced to determine if the cells taken from a patient exhibit mutated or dominant negative p53, and if said cells could be made to undergo apoptosis, and thus cell death, after treatment of said individual with a chemotherapeutic agent, followed by determining which of any of the remaining TGF-beta, p16 or p27 would function in said apoptotic cells in order to attach a significance to the labeling of the tissue sample after exposure to the antibodies directed to TGF-beta, p16 and p27.

Chang et al (Cancer Research, 1999, Vol. 59, pp. 3761-3767) teach that the chemotherapeutic induction of a senescence-like phenotype versus the induction of cell death in human tumor cell lines are independent processes. Chang et al teach that the overall outcome of exposure of chemotherapeutic agents is determined by a combination of factors responsible for the independent induction of cell death versus the senescence-like terminal differentiation such as the amount and the duration of exposure to the chemotherapeutic agent. Chang et al teach that the most common outcome of the treatment of human tumor cell lines is the induction of a senescence-like phenotype and mitotic cell death which contrasts with than apoptosis (page 3766, second column, first full paragraph).

Eymin et al (Oncogene, 1999, Vol. 18, pp. 1411-1418) teach that over expression of p27 is indicative of drug resistance in leukemic cells. Thus, if a sample of tissues or cells was taken from a leukemic patient after the administration of an apoptotic agent and an increase in p27 were noted, was of skill in the art would be forced to determine by other means if the increased expression of p27 were indicative of apoptosis, senescence or terminal differentiation, or if the

increase in p27 were indicating that a selection of drug-resistance leukemia cells was made in said patient by the exposure to the chemotherapeutic agent.

It is concluded that given the breath of the claims to encompass any sample of tissue of cells taken from an individual who has received a chemotherapeutic agent, and the lack of a correlation between the increased expression of p21, p27, p16 and TGF-beta as a marker for apoptotic cells and/or terminally differentiated cells and/or senescent cells, and thus a therapeutic effect, from all the types of cancerous tissue and cells in combination with all types and doses of cancer chemotherapy agents encompassed by the method, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method.

(B)As drawn to a chemopreventative agent

The instant claimed methods are reliant in part upon chemopreventative agents. Nether the specification nor prior art teaches the administration of such a chemopreventative agent to an individual and the removal of cell or tissues from said individual for the determination of an increase in SA-B-gal, p21, p27, p16 or TGF-beta. It is recognized that the art terms "chemoprevention" as intervening at early stages of carcinogenesis to prevent the manifestation of clinically apparent signs or symptoms of cancer, such as the effect of retinoids on early cancer lesions (Dragnev et al, The Oncologist, 2000, Vol. 5, pp. 361-368). However, the induction of terminal differentiation, apoptosis or senescence by retinoids does not fulfill the broad interpretation of the term "chemopreventative agent" which would require the prevention of any cancer, even an early neoplastic lesion. Give the lack of teaching s n the specification and the prior art, one of skill in the art would be forced into undue experimentation in order to practice the claimed method on the evaluation of a response of an individual to a chemopreventative agent, because one of skill in the art would no know how to make such an agent.

The claims are drawn I part to method reliant on obtaining cells or tissue samples from an individual after exposure to a chemopreventative agent. When given the broadest reasonable interpretation, the claims encompass agents which prevent any type of pathology, such as infectious disease, autoimmune disease, genetically inherited disease and cancer in any cell or tissue type.

(C) As drawn to the requirement for an antibody which specifically binds to SA-B-gal

Claims 1, 2 and 4-6 are methods requiring an antibody which binds to SA-B-gal . The specification teaches measurement of SA-B-gal by detecting the blue color formed upon reaction of said antibody with X-gal. The art teaches that B-gal activity at pH 6 is indicative of senescence in cells, but that most cells express a B-gal activity at pH 4 (Dimiri et al, PNAS, 1995, Vol. 92, pp. 9363-9367, page 9364, first column, lines 11-17, under the heading "Results"). The specification does not contemplate the measurement of levels of SA-B-gal by means of an antibody, nor does it provide the structure of the SA-B gal, or a partial structure of the SA-B-gal that would allow one of skill in the art to make an antibody which would stain cells expressing SA-B-gal (pH 6 B-gal) but which would not stain the lysosomal B-gal. In order to practice the instant method one of skill in the art would be required to make and screen for anti-B-gal antibodies having the proper specificity which would not cross react with lysosomal B-gal. However, neither the specification nor the prior art have provided an amino acid sequence for SA-B-gal, and there are no teaching regarding the structural differences between the two enzymes which would give a reasonable expectation of success for the development of an antibody which would differentiate between the two types of B-gal. Because of the lack of teachings in the specification regarding these issues, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed invention.

Applicant argues that the amended claims are now enabled due to the deletion of the claim language requiring detection of apoptosis, terminal differentiation and senescence. This has been considered but not found persuasive. The specification teaches apoptosis, terminal differentiation and senescence as desired therapeutic effects resulting from chemotherapy. The claims persist in lack of enablement because of the unreliability of the art correlating the expression level of the required gene products and therapeutic efficacy of anti-cancer chemotherapy for the reasons set forth above in section A. Applicant argues that numerous chemopreventative agents are know, and thus the specification is enabled for detecting chemoprevention. this has been considered but not found persuasive. The specification provides no objective evidence that the detection of the gene products of the claims is significant for the induction of a chemopreventative state for the reasons set forth above. Applicant argues that the addition of detection by X-Gal staining enables the claims with regard to part C of the rejection

above. this has been considered but not found persuasive. Applicant has not provided any argument regarding an antibody which specifically binds to SA-B-gal, which still persists in the claim language.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
7/9/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER